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VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20850

Re: Comments on Docket No. 00N-1409 – Revision of the Identification of Iontophoresis Device

Dear Sir/Madam:

McKenna & Cuneo, L.L.P. hereby submits the following comments on behalf of our client, Empi, Inc. ("Empi"), in response to the Food and Drug Administration's ("FDA's") proposed change in the classification regulation identifying an iontophoresis device. The proposal was published at 65 Fed. Reg. 50949 (Tuesday, August 22, 2000).

Our client, Empi, is a manufacturer and distributor of iontophoresis devices and of electrodes intended for use with iontophoresis devices. Empi believes that it holds a significant share of the market in iontophoresis devices and electrodes. The company's business would be seriously adversely impacted by the proposed regulation if it were to be finally promulgated in anything like its proposed form.

BACKGROUND AND INTRODUCTION

On May 28, 1976, the Medical Device Amendments ("MDA") to the Federal Food, Drug, and Cosmetic Act (the "Act") were enacted. The MDA, among other things, required the FDA to classify all the medical devices which were in commercial distribution prior to the enactment date ("pre-MDA" or "preenactment") into one of three regulatory classes based upon the regulatory controls needed to provide reasonable assurance of the safety and effectiveness of each device. FDA was commanded by the MDA to appoint and use panels of experts in the field to

assist it in that task. FDA was required to appoint panel members with relevant scientific and medical knowledge, as well as personal experience, to make classification recommendations to the agency.

The three regulatory classes defined in the MDA are: Class I for those devices presenting the least risk and which could be regulated adequately by the general controls, such as Good Manufacturing Practices and Medical Device Reporting; Class II for devices requiring special controls such as performance standards or guidelines in addition to the general controls to achieve adequate regulation; and Class III for those devices requiring premarket approval to achieve adequate regulatory control.

As a result of its classification activities and the panel recommendations, FDA classified iontophoresis devices in a regulation codified at 21 C.F.R. § 890.5525 (see 48 Fed. Reg. 53032 (Wednesday, November 23, 1983) at 53052). That regulation contains two definitions of iontophoresis devices intended for different uses. One definition places into Class II iontophoresis devices either for use in introducing ions from soluble salts or other drugs to induce sweating for diagnosing cystic fibrosis or for use with any drug adequately labeled for iontophoretic administration with the device. Iontophoresis devices labeled for introducing ions from soluble salts for any other purpose or for introducing any other drug are classified into Class III.

FDA apparently proposes to eliminate the Class III definition of an iontophoresis device which currently is published at 21 C.F.R. § 890.5525(b) and to modify the definition of the Class II device which currently is published at 21 C.F.R. § 890.5525(a).

The practical effect of FDA's proposal would be to treat all iontophoresis devices which are simply labeled for delivery of ions from a solution containing a salt as post-MDA new devices automatically classified by statute into Class III. Such devices must have an approved premarket approval ("PMA") application or be reclassified before they can be marketed. Currently marketed devices would have to be either relabeled for the cystic fibrosis diagnosis indication or removed from the market until they obtain PMA approval.

As a rationale for its current proposal, FDA claims that there were no pre-MDA (preenactment) devices which meet the Class III definition. That statement is not true, as is well demonstrated in the device classification administrative record

(e.g., discussions of pre-MDA corticosteroid, lidocaine, and fluoride administration by iontophoresis), in FDA's own facility inspection files, and in a lawsuit (as well as a subsequently issued 510(k) substantial equivalence letter) in which the agency stipulated that a preenactment iontophoresis device existed for the specific purpose of treating hyperhidrosis by sweat inhibition.

As a further rationale for the proposal, FDA also claims that the Class III definition had the "unintended consequence" of placing iontophoresis devices into Class III when they are intended for use to administer drugs not labeled for iontophoretic delivery. That assertion is also false. The agency's own final classification regulation preamble clearly states that the agency intended to accomplish that very result with respect to at least two known pre-MDA devices. (Frankly, given FDA's rationale for Class III treatment, we are not certain why iontophoresis devices for cystic fibrosis diagnostic use were treated differently because, to the best of our knowledge, neither pilocarpine hydrochloride nor any other drug or salt either has been, or currently is, labeled for iontophoretic delivery for that use either.)

For the reasons explained more fully in these comments, the agency will without doubt be acting arbitrarily and capriciously if it proceeds with this proposal. Our substantive comments on the proposal follow.

I. FDA should withdraw the proposal as ill considered, contrary to fact, contrary to FDA's own administrative record, and inconsistent with the current regulation.

A. FDA's own iontophoresis classification administrative record clearly demonstrates that at least two pre-MDA iontophoresis devices were intentionally placed in the Class III category.

FDA set up multiple panels of experts to begin recommending the classification of then commercially marketed medical devices before passage of the Medical Device Amendments of 1976 ("MDA"). The panels were reconstituted and continued their activities after the passage of the MDA. Three of those panels considered iontophoresis devices intended for at least three different specific uses and made recommendations to FDA. The three specific uses considered were: (1) for diagnosing cystic fibrosis by administering pilocarpine to produce sweat (by the Physical Medicine (Physiatry) panel); (2) for anesthetizing the intact tympanic membrane with lidocaine and epinephrine (by the Ear, Nose, and Throat panel);

and (3) to apply fluoride to the teeth to reduce hypersensitivity and for cavity prevention (by the Dental panel). In addition, the Physical Medicine panel discussed other well known pre-MDA iontophoresis device uses for introducing ions from soluble salts to treat numerous other medical conditions, including the iontophoretic administration of corticosteroids.

We have obtained, from FDA's own records, copies of portions or all of the transcripts of several classification panel meetings. They include transcripts for the Physical Medicine panel meeting on Friday, July 7, 1978 ("Transcript PM 1"); the Physical Medicine panel meeting on December 12, 1979 ("Transcript PM 2"); and the Ear, Nose, and Throat panel meeting on November 6, 1978 ("Transcript ENT 1").

At a Physical Medicine panel meeting on Friday, July 7, 1978, Dr. Justis F. Lehman, a panel member and Professor and Chairman, Department of Rehabilitation Medicine, University of Washington Hospital, Seattle, Washington, made an extended presentation concerning well known clinical uses of iontophoresis devices. While he was not particularly supportive of the effectiveness of many of those uses, he characterized iontophoresis as "widely used in clinical practice for many years" (Transcript PM 1, page 128). He further stated, "[w]hen I went to Seattle, everyone in town was doing iontophoresis" (Transcript PM 1, page 137.) He was asked when administration of histamine by iontophoresis had occurred and responded, "[o]h. that was at least one or two decades ago" (Transcript PM 1, page 138). When asked about specific physical medicine uses of iontophoresis devices, Dr. Lehman replied, "[t]he drugs are used – cortisone preparations, what else . . . [t]o increase vascularity, to administer anesthetics, to relieve muscular spasms" (Transcript PM 1, page 139).

At a subsequent Physical Medicine panel meeting, on December 12, 1979, iontophoresis devices were again discussed. Dr. Philip Arnold, a guest at the meeting, stated that "historically in physical medicine 25 or 30 years ago there was much more use of iontophoresis for 'delivery of medication' than there is now" (Transcript PM 2, page 19). The panel was then referred to and discussed a chapter in the book, Therapeutic Electricity and Ultraviolet Radiation, edited by Sidney Licht, M.D. (Waverly Press, Baltimore, 1967). That chapter was authored by Ronald Harris and was entitled "Iontophoresis" (hereafter called the "Harris reference"). A copy of the chapter is attached as Exhibit 1. It reviews numerous preenactment uses of iontophoresis with different ion producing salts, metals, and drugs. The Harris reference was cited as reference number 1 in the preamble to

FDA's proposed iontophoresis device classification regulation (44 Fed. Reg. 50620 at 50622 (Tues., Aug. 28, 1979)).

While the panel had concerns about the safety or effectiveness of many of the uses discussed in the Harris reference, they did not challenge the fact that iontophoresis devices were commercially sold and used for such uses before the MDA. In fact, the Harris reference and related discussion (including a discussion of iontophoresis for sweat inhibition to treat hyperhidrosis) prompted the panel to suggest the Class III classification for "other uses" than "cystic fibrosis diagnosis, application of fluoride in dental, and application of anesthetic topical (sic) tympanic membrane in ENT," all of which were recommended for Class II. (Transcript PM 2, pages 20-29).

The Ear, Nose, and Throat panel met on November 6, 1978 and also discussed iontophoresis devices. At that meeting, Dr. Brummett led an extended discussion of the use of an iontophoresis device for anesthetizing the tympanic membrane with lidocaine and epinephrine (Transcript ENT 1, pages 4-22). In the course of that discussion, the length of time that such products had been on the market was discussed. Mr. Bruce, an attendee from Xomed, indicated, "Xomed has been marketing this one for at least four years" (Transcript ENT 1, page 20). Mr. Bruce also discussed the labeling for the device indicating that it was very specific concerning the chemicals to be used, i.e., "[t]he labeling on the device and all of our own instruction manuals and advertising clearly states (sic) that only these two specific materials, in those concentrations, be used" (Transcript ENT 1, page 197). When asked what the labeling said, Dr.Tonndorf, a panel member apparently reading directly from the labeling, said, "[m]ix equal volumes of 4 percent lidocaine and 1 to 1000 epinephrine. Shake thoroughly before using." (Transcript ENT, page 197.) In its current proposal, FDA has presented no evidence whatsoever to refute this clear testimony which provides positive evidence of a specific preenactment iontophoresis device labeled and marketed for use with a drug that was not labeled for iontophoretic use.

The Dental Panel considered an iontophoresis device for application of fluoride to reduce hypersensitivity and for cavity prevention. The panel summarized its deliberations in a "Supplementary Data Sheet, Summary of Reasons for Classification." A copy of that document is attached as Exhibit 2. The Dental panel identified no serious risks and proposed that the device be classified in Class I when used for the described purpose. It had no question that the device was

commercially distributed pre-MDA for the identified use. FDA has not presented any evidence to rebut this evidence either.

Based at least in part on the discussions recorded in the panel transcripts and the Supplementary Data Sheet referred to above, in the Federal Register on August 28, 1979 (44 Fed. Reg. 50520), FDA published proposed classification regulations for the iontophoresis device. In that proposal, the agency proposed four separate classification subsections, one for each of the three above described specific uses, each of which was proposed for Class II, and a catchall fourth subsection for other uses which would introduce soluble salts (i.e., medications) for therapeutic or diagnostic uses.

During the comment period on the classification proposal, FDA had yet another preenactment use of iontophoresis devices called to its attention, that of sweat inhibition. See 48 Fed. Reg. 53032 (Wednesday, November 23, 1983) at 53045. (See also, the discussion of the device in the Physical Medicine panel meeting on December 12, 1979, Transcript PM 2, pages 23-28.)

In the preamble to promulgation of its final classification, in the November 23, 1983 Federal Register notice, FDA specifically stated that it was eliminating the proposed classification regulations for the tympanic membrane and dental uses. The agency said those uses were being incorporated into the Class III definition because there were no drugs labeled for those uses. As the agency clearly stated:

> At the present time, the agency is unaware of any marketed drug that has labeling providing adequate directions for use with an iontophoresis device for the dental application of fluoride or the anesthetizing of the intact tympanic membrane. Therefore, the effect of the change in the identification of the device is to classify into class III iontophoresis devices for these two uses. (Emphasis added.)

(48 Fed. Reg. 53032 at 53045). The agency did not challenge the preenactment commercial sale of devices for those uses. Thus, it confirmed that they were at least two pre-MDA devices which came within the Class III definition.

In publishing its current proposal, the agency has essentially claimed that the above administrative record either is false or does not exist. It has presented no evidence whatsoever in support of its bald assertion that creation of the Class III

iontophoresis device identification was erroneous. It has made no attempt to explain why the contemporaneous experts who reviewed, discussed, and recommended the original device classifications, in part based upon their own personal experience, were incorrect in stating that such pre-MDA commercially distributed devices existed and were widely used. Furthermore, the above quoted preamble directly contradicts FDA's assertion, in the new proposal, that "the definition had the unintended consequence of placing into class III all those iontophoresis devices intended for use with a drug whose labeling cannot bear adequate directions for the device's use with the drug (i.e., a drug that had not been approved for iontophoretic delivery" (65 Fed. Reg. 50949 at 50950). (Emphasis added.)

In view of all the above described, unrefuted contrary evidence in its own administrative record, FDA cannot proceed with the current proposal. To do so would be the height of arbitrary and capricious action in violation of the Administrative Procedure Act (5 U.S.C. §§ 551 *et seq.*).

B. FDA admitted, in settling litigation and in clearing a device for marketing, that yet another pre-MDA commercial use of an iontophoresis device existed that came within the Class III definition.

In response to a premarket notification ("510(k)") under section 510(k) of the Act (K831320), on July 5, 1983, FDA declared General Medical Company's ("General Medical's") Dryonic device for iontophoresis with tap water to treat hyperhidrosis by inhibiting sweat "not substantially equivalent" and therefore subject to premarket approval. General Medical sued the agency in the U.S. District Court for the District of Columbia, Civ. No. 83-3314, asking the court to declare that the device could be lawfully marketed as a substantially equivalent device. After discovery and General Medical's Motion for Summary Judgement, FDA agreed to a stipulated dismissal of the suit in which the agency admitted that a pre-MDA iontophoresis device for hyperhidrosis treatment existed. A certified copy of the "Stipulation", filed October 10, 1984, a copy of the "Stipulation and Order of Dismissal", filed November 19, 1984, and a certified copy of the court's Docket Index for the case showing those filings are attached as Exhibit 3.

Shortly before FDA agreed to the above stipulations, the agency issued a "substantial equivalence" letter to General Medical permitting marketing of the Dryonic device. In that letter, dated September 29, 1984, clearing 510(k) number

K831320 as a Class III device, FDA admits that its own archival records provided evidence that the Fischer Model 2800 galvanic stimulator was represented and sold for iontophoresis to treat hyperhidrosis as early as 1959, long before the MDA. A copy of that substantial equivalence letter was filed in the District Court action by FDA. Certified copies of the Notice of Filing, the letter, its attachments, and the Certificate of Service, all from the court's records, are attached as Exhibit 4. The labeling of the Fischer device also demonstrates several other pre-MDA uses of iontophoresis devices in commercial distribution. They are as follows: iontophoresis with copper sulfate to treat fungus infections of the extremities, with common salt to treat bromidrosis, with sodium salicylate to treat arthritis, with plain water to treat edema, and with imadyl unction to treat bursitis and tenosynovitis.

In light of the above admissions by, and court order involving, FDA, the agency is legally estopped from now asserting that no pre-MDA devices existed which met the Class III iontophoresis device definition. The stipulation and admission clearly refute FDA's sole rationale for its proposed action. Therefore, the proposal should be withdrawn.

C. Labeling and advertising of other devices and publications further demonstrate preenactment commercial distribution of iontophoresis devices for uses within the Class III definition.

At least some pre-MDA iontophoresis devices were merely labeled for "iontophoresis" and did not specify which of the many well known uses, such as those described in the Harris reference, for which they were intended. Another description of the widely known pre-MDA uses of devices simply labeled for "iontophoresis" appeared in the article, "Use of Low Voltage Electrotherapy and Electromyography in Physical Therapy," Amrein et al., Physical Therapy, Vol. 51, Number 12, December 1971, page 1283. A copy of that article is attached as Exhibit 5. Any device labeled simply for "iontophoresis" is, by definition, labeled for introducing ions of soluble salts or drugs into the body even if those salts or drugs are not labeled for such a route of administration. Therefore, since their use is not specifically limited to administration of adequately labeled drugs, such devices clearly fall within the category described as intended for introducing ions from salts or drugs not adequately labeled for iontophoretic administration (i.e., the current Class III definition).

One example of a pre-MDA device simply labeled for iontophoresis is the Fischer Model 2900 device. FDA is, and long has been, well aware of the Fischer Model 2900 device. It was brought to the agency's attention in General Medical's U.S. District Court litigation against the agency (Civ. No. 83-3314, D.D.C. 1983), and labeling for it was included in the Appendix to General Medical's Motion for Summary Judgment in that litigation. Attached Exhibit 6 is an extract from that Appendix. The device was also referenced in FDA's substantial equivalence letter, dated September 29, 1984, clearing 510(k) No. K831320 (Exhibit 4). Finally, in response to an FOI Act request by a member of our firm, FDA produced an Establishment Inspection Report ("EIR") of R. A. Fischer & Co. from September 1969 and labeling obtained during that inspection. Excerpts from those records relating to the Model 2900 are attached as Exhibit 7.

Furthermore, FDA's own inspection files concerning a September 11, 1959 inspection of R. A. Fischer & Co. also demonstrate additional pre-MDA iontophoretic uses of another device, the Fischer Model 2800 Galvanic Generator, referenced in FDA's substantial equivalence letter (Exhibit 4). Excerpts from the FDA's inspection files are attached as Exhibit 8. (Unfortunately, it appears that FDA failed to produce page 2 of Exhibit I-17 to its EIR in response to our firm's FOI Act request.) Nevertheless, at a minimum, the documents demonstrate pre-MDA marketing of the product for iontophoresis with copper sulfate to treat fungus infections of the extremities, epsom salts to treat hyperhidrosis, common salt to treat bromidrosis, sodium salicylate to treat arthritis, plain water to treat edema, imadyl unction to treat bursitis and tenosynovitis, and possibly other substances to treat other conditions. In light of this additional evidence of pre-MDA uses from FDA's own files, withdrawal of the proposal is the only course open to FDA.

Empi has also searched for additional proof of commercial distribution of iontophoresis devices for uses falling within FDA's Class III definition. Copies of the documents located in that search are attached as Exhibit 9. We believe they further and conclusively demonstrate that numerous devices which fall within the Class III definition were in commercial distribution prior to the enactment of the MDA. We have not sought affidavits supporting actual sales of all the devices shown in Exhibit 9, because we believe the other evidence already presented or described elsewhere in these comments adequately demonstrates the falsity of FDA's assertion that no Class III pre-MDA devices existed. If additional evidence becomes necessary, we are convinced that supporting affidavits can be obtained for at least some of the devices represented in Exhibit 9.

D. The proposal, if adopted as proposed, will make the resulting regulation internally inconsistent, and will not accomplish the result apparently sought by FDA.

In the preamble to the proposal, FDA indicates that it intends to eliminate the Class III definition and to revise the Class II definition by eliminating a sentence. However, in the operative amending language of the proposal, FDA proposes to add the revised definition at the end of the current regulation as new subsections (d) and (e). The proposal does not delete the current definitions contained in subsections (a) and (b) or the PMA date provision in subsection (c). As a result, the proposed amendment would create two non-identical Class II definitions and retain the current Class III definition. This result, when taken together with FDA's assertions in the preamble of its intent in proposing the amendment, fails to give adequate notice of FDA's true intention. The public has been inadequately notified of FDA's real intended language and content in any resulting final regulation.

SECTION I SUMMARY

For all of the reasons discussed above, we believe that the only reasonable course of action open to the agency is to withdraw the proposal. Any attempt to finalize it will clearly constitute arbitrary and capricious action by the agency in the face of its own unrebutted administrative record, including descriptions of personal experience with pre-MDA devices within the Class III definition by classification panel experts and witnesses. Further, the agency is estopped from denying the existence of a pre-MDA iontophoresis device for treatment of hyperhidrosis. The agency also classified that device as a Class III device in a substantial equivalence letter after admitting the existence of a legal predicate device in a stipulated court action dismissal. Labeling and advertising for pre-MDA products, including some obtained directly from FDA's own inspection records, show that pre-MDA devices meeting the Class III definition were neither rare nor experimental. Finally, the proposal is internally inconsistent and fails to adequately notify the public as to the agency's real intended changes to the regulation. These defects in the proposal cannot be corrected by a reproposal, much less by adoption of this or an amended change without a reproposal. The agency must simply return to the status quo until it is prepared to either call for PMAs on the Class III devices or reclassify them.

II. If FDA promulgates a final regulation based on the current proposal, it should delay the effective date of the regulation for two years rather than the proposed 180 days.

A. FDA has presented no evidence to support its assertion that previously cleared iontophoresis devices can simply be relabeled for use in diagnosing cystic fibrosis without raising significant safety or effectiveness issues. That assumption is wrong, and the proposed phase in time is unworkable as a result.

In the preamble to its current proposal, FDA has simply asserted, without any supporting evidence, that most or all of the previously cleared Class III iontophoresis devices can simply be relabeled for diagnosis of cystic fibrosis. The agency further indicated that the change could be made without submission of new 510(k)s. Such a position necessarily implies that the relabeling would not have a significant effect on the safety or effectiveness of the devices.

Not only is there no evidence in the record to support the agency's assertions, we present evidence in these comments that the agency's position is wrong. As explained in the affidavit of Donald Maurer, attached as Exhibit 10, at least some of the low output devices on the market will be unable to effectively drive sufficient pilocarpine or any other effective substance into the body to produce sufficient sweat needed for the diagnosis. (See Exhibit 10.) Furthermore, many, if not most, of the iontophoresis electrodes now on the market for use with cleared devices are designed for use with liquid drugs or salt solutions. A review of FDA's publication, "Approved Drug Products with Therapeutic Equivalence Evaluations, 20th Edition" (2000) (the "Orange Book") and its most current Supplement 10 (October 2000) demonstrates that there are no current approved liquid dosage forms of pilocarpine or pilocarpine hydrochloride as a single ingredient drug product. Copies of the pilocarpine approved products entries from the agency's current Orange Book are attached as Exhibit 11.

The only approved liquid dosage form containing pilocarpine is a combination drug, Betoptic Pilo, which also contains betaxalol hydrochloride, a beta blocker. It would not be appropriate to use that product for cystic fibrosis diagnosis because of both the unwanted pharmaceutical action and the possible serious side effects attendant the administration of a beta blocker. Side effects of betaxalol hydrochloride include the possibility of death due to severe broncospasm in patients with asthma and (rarely) death in association with cardiac failure. See the

"WARNING" section from the labeling for Betoptic S, a single active ingredient drug produced by the same manufacturer which contains the same amount of betaxalol hydrochloride as Betoptic Pilo. A copy of the Betoptic S labeling contained in the Physicians' Desk Reference, 54th Edition (2000) ("PDR") is attached as Exhibit 12. The labeling for Betoptic Pilo is not contained in either the PDR, the Physicians' Desk Reference for Ophthalmology, 28th Edition (2000) ("Ophthalmic PDR"), or Alcon Laboratories, Inc.'s web site (as of December 13, 2000). We requested a copy of the most recent approved labeling for Betoptic Pilo from FDA under the FOI Act (request number F00-21338). We have been informed by FDA, in a response, dated December 4, 2000, that, even though the NDA was approved on April 17, 1997, "[t]he final approved labeling is not yet available for the product." Our inquiries lead us to believe that the NDA holder may not yet be marketing the product. However, we have no reason to believe that the "WARNING" section in the final approved Betoptic Pilo labeling will be different from that of Betoptic S concerning the possible adverse effects of the beta blocker constituent of the drug.

Two other approved dosage forms containing pilocarpine, the Ocusert Pilo-40 and Ocusert Pilo-20 are special ophthalmic extended release drug delivery systems (ocular inserts designed for continuous release of drug). They clearly are not usable for iontophoresis. See the product labeling for those products from the Ophthalmic PDR, which is attached as Exhibit 13.

Another approved dosage form containing pilocarpine is an oral tablet, a dosage form clearly not suitable for iontophoretic administration. See the product labeling for Salagen tablets from the PDR, which is attached as Exhibit 14.

Finally, there is an approved gel dosage form of pilocarpine. See the product labeling for Pilopine HS from the Ophthalmic PDR, which is attached as Exhibit 15. That dosage form is not labeled for iontophoretic administration or for cystic fibrosis diagnosis. Nevertheless, it might be suitable for off label use by that type of administration in a system which has electrodes designed for use with gel form drugs. However, as indicated in the Maurer affidavit (Exhibit 10), many, if not most, of the currently marketed electrodes are designed for use with liquids and are not suitable for delivering gel form drugs. Those electrodes would deliver pilocarpine from a gel form only in a hollow ring around the edges of the electrode, a phenomenon called the "edge effect," which could lead to false negative diagnoses. Furthermore, as also stated in the Maurer affidavit, some cleared iontophoresis devices would be incapable of driving an effective amount of pilocarpine into the tissue when a gel form is used.

Empi is not aware of any other approved drugs or any ions of soluble salts which either are labeled for, or actually will work by, iontophoretic administration to diagnose cystic fibrosis. (See also Maurer affidavit (Exhibit 10).

None of the pilocarpine containing drugs which have been approved by FDA contain an approved indication for diagnosis of cystic fibrosis. In addition, none of them are approved for iontophoresis as a route of administration. Nevertheless, iontophoresis devices intended for administration of pilocarpine for cystic fibrosis diagnosis (an off label use of the drug) are well documented as pre-MDA devices. In fact, off-label iontophoretic administration of pilocarpine to diagnose cystic fibrosis has become the standard of medical care. It would be irresponsible of FDA to take any action which would discourage or prevent that use. However, in light of those facts, we fail to see any logical reason why FDA should have concern about maintaining a classification regulation which permits marketing of iontophoresis devices for off label administration of other approved drugs or other ionic solutions. Devices for those uses have been thoroughly documented as pre-MDA commercially distributed devices. In fact, we have difficulty understanding why the cystic fibrosis use was placed in Class II, while all other well documented pre-MDA off-label uses to administer other drugs, particularly corticosteroids, and the lidocaine/epinephrine combination, have been placed in Class III.

Iontophoretic administration of corticosteroids, particularly dexamethasone sodium sulfate, to treat inflammation and accompanying pain have likewise become the standard of care in physical therapy. It also would be irresponsible of FDA to take any action which would limit or prevent iontophoresis devices and electrodes from being used, off label, by licensed practitioners for those purposes.

Due to the difficulty in predicting which FDA cleared Class III iontophoresis devices and which electrodes will work satisfactorily with one of the currently approved pilocarpine drug products, we believe it would be necessary for FDA to require 510(k) submissions on both the devices and the electrodes to demonstrate proper functioning for the cystic fibrosis indication before permitting the labeling change. The proposal does not advise the public of the possible need to submit new 510(k)s. To give adequate notice, we believe a reproposal, at a minimum, would be necessary if FDA wants to proceed with a relabeling requirement. Furthermore, we believe the proposal should be withdrawn for the reasons listed above in Section I. Therefore, it is highly unlikely that the industry will be willing to incur the expense of preparing new 510(k)s before any final regulation is issued which necessitates such action. Submission and review of a large number of 510(k)s on currently

marketed iontophoresis products would undoubtedly cause a backup in the agency's review process. It is highly unlikely that all the submissions could be prepared, submitted, and cleared within the proposed 180 day period before the final regulation would become effective. Therefore, we believe that FDA should delay the effective date of any final regulation based on the current proposal or any reproposal for at least two years from publication of the final regulation. Such a grace period would permit the needed actions to occur without undue disruption of the iontophoresis device and electrode marketplace.

B. The time for implementing labeling and packaging changes for both iontophoresis devices and electrodes, particularly those already in finished goods or distribution centers, would be insufficient with only a 180 day delay in effective date.

Due to the many uncertainties arising from the FDA proposal, it is unlikely that any manufacturers will begin any relabeling activities until after a final regulation is promulgated. Before that time, the industry will not know whether the rulemaking will even proceed, whether simple relabeling will suffice, or whether new submissions and, possibly, new designs will be required. In addition, even if the changes were to be in labeling only, the industry will not know the final requirements until a final regulation issues.

Once the labeling requirements are known, the industry must draft the appropriate labeling, have it reviewed and approved through its quality system, and purchase or print the new labeling. Then, it must implement use of the revised labeling in both new production and at least a portion of already finished goods. Since iontophoresis devices do not carry expiration dates, and electrodes either do not carry expiration dates or have relatively long expiration dating (see Maurer affidavit (Exhibit 10)), at least part of the finished goods supplies which are still in the hands of the manufacturer will have to be unpackaged, relabeled, and repackaged. Any such activities must also be carried out without disrupting supplies to the market. Therefore, it is highly unlikely that all the necessary relabeling could be completed within the proposed 180 day grace period.

Many of the currently marketed iontophoresis electrodes may be unsuitable for administration of currently approved forms of pilocarpine. If iontophoresis devices must be labeled for the cystic fibrosis indication only, any such electrodes will have no legal use. Presumably, FDA would insist that any such electrodes be withdrawn from the market not later than the effective date of the new regulation.

Because these electrodes do not present any health hazard, there is no compelling reason for the agency to insist upon a short phase in time for any new regulation. A short phase in would cause the industry the extra expense of scrapping those electrodes. The industry cannot anticipate such a situation because of the substantial problems with the agency's proposal as detailed above in these comments. The form and timing of any final agency action on this proposal are highly unpredictable for those reasons.

Two years is a much more reasonable time for a phase in of any new labeling requirement. If FDA insists on too short a time for the activities necessary to relabel and repackage, it will significantly raise their cost and will simultaneously increase the probability that mistakes will be made. Such mistakes could affect the safety or effectiveness of the products. A longer phase in time would permit more of the finished goods to be sold as is while stocks of newly manufactured products with the revised labeling enter finished goods. Once sufficient numbers of relabeled products are in finished goods and manufacturer distribution centers, any remaining inventory of the product with old labeling could be relabeled without seriously disrupting the supply. The products with old labeling present no health or safety hazard if distributed as is. Therefore, FDA should not impose any time frame which could create such a hazard. Forcing a relabeling operation to occur too quickly could cause that activity to damage otherwise safe and effective products.

C. Another relabeling option for manufacturers, by obtaining approval of specific drugs for iontophoretic administration, cannot be completed within the proposed 180 day grace period, even if such a plan is already in progress.

Empi has undertaken a project to obtain a new drug approval ("NDA") necessary to label a specific drug product for iontophoretic administration with its device. Once such an NDA is approved, Empi can submit a 510(k), as a Class II device, for permission to relabel its iontophoresis device for administration of the approved drug product.

Empi began such a project in July 1996 with an initial pre-IND meeting at FDA concerning iontophoretic administration of a lidocaine/epinephrine combination drug product. Since that time, the following events have occurred in seeking the drug approval:

May 1997 Pre-IND meeting. New dermal irritation study required.

June-July 1997	Laboratory Benchtop Testing
Aug.-Sept. 1997	Pre-clinical Animal Study
Oct.-Dec. 1997	IND preparation and submission
Jan. 1998	Clinical studies begun
Feb. 1998	Phase I pharmakinetic ("pK") Study
April 1998	pK Results & Final Report
May 1998	IND Amendment preparation/submission for Phase II
June-Aug. 1998	Hold on Phase II Study awaiting FDA response. IND Amendments submitted.
Aug. 1998	Initiate Phase II Study
Oct. 1998	FDA letter concerning Phase II studies
Feb. 1999	Empi response to FDA letter
Mar.-May 1999	Draft Phase III Protocols and IND Amendment
June 30, 1999	FDA end of Phase II meeting
July-Nov.1999	Prepare/Submit additional IND amendments responding to Phase II meeting questions
Oct.-Dec. 1999	Revise Phase III Protocols & add pediatric protocol
Jan. 2000	Submitted Protocols for Phase III studies
Feb.-Mar. 2000	Begin Phase III venipuncture & shave removal studies
Mar. 2000	FDA letter requesting additional information
Mar. 2000	Initiated two Phase III studies
Apr. 2000	Submitted pediatric study Protocol

June 2000	Submitted protocol for in vitro stability study
July 2000	Began Phase III pediatric venipuncture study
Sept. 2000	Initiated in vitro stability testing
Oct. 2000	Submitted and initiated comparative Protocol
Nov. 2000	Initiated pediatric Protocol. Submitted requested information to FDA

As one can readily see, while Empi has proceeded diligently on the project for nearly 4½ years, several steps remain before an NDA approval and subsequent 510(k) clearance can be obtained. It is not unlikely that these steps will extend beyond the promulgation date, if any final regulation is issued based upon the current proposal. If the implementation time is too short after final regulation issuance, then Empi would be faced with the need for, and expense of, relabeling its products twice.

Furthermore, some electrodes which may be unsuitable for administration of an approved form of pilocarpine are suitable for lidocaine/epinephrine administration. Therefore, to keep those products available, it might become necessary to submit and receive approvals for one or more IDEs on the iontophoresis device and/or electrodes and to relabel the products as investigational devices until the new NDA approval and subsequent 510(k) clearance are obtained. Thus, three relabelings and additional device application submissions could be necessary if FDA goes forward with its proposal and does not permit a grace period significantly longer than the proposed 180 days. FDA should not force the industry to incur such costs when there is no demonstrated, or even alleged, public health risk presented by the current situation. The likelihood of such bizarre regulatory results could be significantly reduced by a two year delay in the effective date of any new regulation.

SECTION II SUMMARY

If FDA does proceed with a final regulation based on this proposal, it will have effects significantly greater than those contemplated by the agency in its preamble to the proposal. Those effects could include elimination of any legal use for many currently marketed iontophoresis electrodes. New investigational device exemption applications might be required to continue projects currently underway.

Furthermore, it is highly likely that new 510(k) clearances would be required. At least, significant relabeling and repackaging would have to be undertaken unless the effective date of the regulation is delayed for at least two years from its promulgation date.

CONCLUSION.

For all the reasons stated above, FDA should withdraw its proposal to revise the classification of the iontophoresis device. To continue with the proposal will be clearly arbitrary and capricious action by the agency.

Should the agency continue with any reproposal or final regulation that will require relabeling of products, and possibly new clearances and/or market withdrawal of some products, a delay in the effective date of at least two years after promulgation of a final regulation should be established.

Sincerely,

Donald R. Stone

DRS/drs
Enclosure(s)
cc: H. Philip Vierling – Empi, Inc.
Deborah L. Jensen – Empi, Inc.
Joel Aaberg, Esq. -- Empi, Inc.